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Combined texture analysis of diffusion-weighted imaging with conventional MRI for non-invasive assessment of *IDH1* mutation in anaplastic gliomas

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AIM: To examine whether texture analysis (TA) of diffusion-weighted imaging (DWI) combined with conventional magnetic resonance imaging (MRI) could non-invasively predict isocitrate dehydrogenase 1 (*IDH1*) mutational status in anaplastic gliomas.

MATERIALS AND METHODS: Fifty-two patients with histologically confirmed anaplastic glioma was reviewed retrospectively. Conventional MRI was evaluated using the Visually Accessible Rembrandt Images (VASARI) scoring system. TA of DWI based on the entire tumour volume was compared between *IDH1*-mutant and wild-type tumours by using unpaired Student's *t*-test. Receiver operating characteristic curve (ROC) and logistic regression were used to assess their diagnostic performance.

RESULTS: Significant statistical differences in VASARI features and TA of DWI were observed between *IDH1*-mutant and wild-type tumours (all $p<0.05$). Using multivariable logistic regression, the proportion of the tumour that was non-enhancing and the entropy of apparent diffusion coefficient (ADC) were found to possess higher prediction potential for *IDH1* mutation with areas under the ROC curve (AUC) of 0.918 and 0.724, respectively. A combination of these for the identification of *IDH1* mutations improved the AUC to 0.954, with a sensitivity and a specificity of 81% and 96%.

CONCLUSIONS: The combined assessment of the conventional MRI and TA of DWI were useful for predicting *IDH1* mutation in anaplastic gliomas.

Introduction

Anaplastic gliomas (AGs), classified as World Health Organization (WHO) grade III, are aggressive brain tumours. The clinical characteristics, radiological features, and genetic changes all play important roles in determining the prognosis of patients with AGs.[1] Mutation in the isocitrate dehydrogenase 1 (*IDH1*) gene at R132 is an important

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molecular event and plays a significant role in gliomagenesis.[1] The value of detecting *IDH1* mutational status has been reported in diagnostic and prognostic studies.[2] Mutations in the *IDH1* gene were associated with improved outcomes in patients with high-grade gliomas.[3] Hartmann *et al.*[4] reported that patients with *IDH1* wild-type anaplastic astrocytomas exhibit worse prognoses than *IDH1*-mutated glioblastomas. Furthermore, previous studies have reported that *IDH1* mutations were correlated with a higher rate of response to temozolomide.[5] Currently, immunohistochemical staining and DNA sequencing are the most common methods for determining the *IDH1* mutational status in gliomas; however, both sequencing and immunohistochemical examinations require tumoural tissues and the biopsy has limitations due to the inherently invasive procedure, sampling errors, and variability in interpretation, especially with stereotactic. Neither of them can offer preoperative detection of *IDH1* gene status. Therefore, a non-invasive method is required to detect *IDH1* mutational status before surgery or biopsy.

Previous studies have demonstrated the correlation between *IDH1* status and the radiological features of glioma, in that tumours with *IDH1* mutation are more likely to have a larger proportion of non-enhancement, a sharp border, and be sited in the frontal lobe.[6] A comprehensive feature set known as the Visually Accessible Rembrandt Images (VASARI) was developed in 2008 for more accurate and reproducible assessment of conventional magnetic resonance imaging (MRI) features of gliomas. The VASARI scoring system includes 30 semantic descriptors of imaging features of brain tumours. The imaging features with corresponding criteria clustered by categories related to lesion location, morphology of the lesion substance, morphology of the lesion margin, alterations in the vicinity of the lesion, and remote alterations.[7] Zhou *et al.*[8] reported that VASARI features could predict *IDH1* mutation in diffuse lower-grade gliomas. These VASARI features were partly based on the scores of radiologists, the scores can be subject to the variability between different readers and random errors during manual contour tracing.

Diffusion-weighted imaging (DWI) can non-invasively provide direct insight into the microscopic physical properties of tissues through observing the Brownian movement of water and use of ADC values to reflect the cellularity within lesions.[9] Lee *et al.*[3] reported that histogram analysis of DWI based on the entire tumour volume were useful for distinguishing *IDH1*-mutant and *IDH1* wild-type high-grade gliomas. Anaplastic gliomas exhibit heterogeneity both genetically and histopathlogically with intratumoural spatial variation in cellularity, angiogenesis, the extravascular extracellular matrix, and areas of necrosis.[10] MRI-based texture analysis (TA) can eliminate subjective assessment of the observer and provide a quantitative measure to assess the distribution of grey-levels within an image to obtain texture features of intra-lesion heterogeneity.[11] There have been reports suggesting that tumour textures presented on conventional MRI images, such as tumour heterogeneity and tumour border diffuseness, correlate with the genetic status of gliomas.[8,12] To authors' knowledge, however, there have been no previous reports concerning the use of volume-based TA of DWI combined with MRI features to distinguish *IDH1* genotypes. This study aimed to explore whether a novel approach, in which the TA of DWI combined with MRI could non-invasively predict *IDH1* mutational status in AGs.

Materials and methods

Patients

The institutional review board approved this retrospective study, and informed consent was obtained from all of the patients. In total, 52 adult patients histologically diagnosed with AG who had undergone surgical treatment from January 2014 to October 2017 were reviewed retrospectively. Patients were included based on the following criteria: (1) all patients were incipient and had not received previous hormone and other treatments, (2) presurgical structural MRI with adequate image quality (T1-weighted, T2-weighted, contrast-enhanced T1-weighted imaging [WI], and DWI) had been performed, and (3) the patients had histopathology-confirmed AG based on the modified WHO grading system. Six patients were excluded for the following reasons: (a) inadequate MRI quality due to the presence of motion artefacts in one or more of the MRI sequences (n=4), (b) lack of the information regarding *IDH1* mutation status (n=2). As a result, 46 patients (25 men and 21 women; mean age, 47.8±12 years; age range, 18–72 years) were included in the study.

Imaging protocol

Images were acquired in the routine clinical work-up on a 3 T MRI system (Magnetom Verio Tim; Siemens, Erlangen, Germany) with a 12-channel head matrix coil. The conventional MRI protocols consisted of the following sequences: axial T1WI and contrast-enhanced T1WI (400 ms repetition time [TR], 2.48 ms echo time [TE], 5 mm section thickness, 230×230 mm field of view [FOV], 320×256 matrix); T2WI (5,090 ms TR, 91 ms TE, 5 mm section thickness, 230×230 mm FOV, 320×320 matrix); fluid attenuated inversion recovery (FLAIR; 8,900 ms TR, 97 ms TE, 2,300 ms inversion time, 5 mm section thickness, 230×230 mm FOV, 256×256 matrix).

DWI was performed in the axial plane with a spin-echo echo planar sequence before injection of contrast material. The imaging parameters used were as follows: 4,800 ms TR, 100 ms TE, average=2, 5 mm section thickness, 1 mm intersection gap, 230×230 mm FOV. The b-values were 0 and 1000 s/mm^2 with diffusion gradients encoded in the three orthogonal directions to generate three sets of diffusion-weighted images. Processing of the ADC map was generated automatically by the MRI system.

Immunohistochemistry staining

Immunohistochemistry was performed on 5-μm-thick sections from paraffin-embedded tumour specimens of all

evaluated patients. Sections were incubated overnight at 4°C with the monoclonal anti-m*IDH1* antibody (MX031; Maixin, Fuzhou, China) that specifically reacts with the mutant *IDH1*-R132, the most common glioma-derived mutation, but not with wild-type *IDH1*. Following incubation with horseradish peroxidase-conjugated secondary antibody, the slides were then stained with the Cytomation En-Vision System horseradish peroxidase (diaminobenzidine) detection kit (Maixin, Fuzhou, China) and counterstained with haematoxylin. Staining was interpreted as positive when 10% of tumour cells showed a strong cytoplasmic staining for m*IDH1*, whereas staining of 10% of tumour cells was counted as a negative finding.[12,13]

DNA sequencing for IDH1 mutation

AGs samples were obtained from each patient during surgery. A portion of the tumour tissue was snap-frozen in liquid nitrogen and stored at −80°C. Tumour DNA was isolated from the frozen blocks by using a QIAamp DNA Blood Mini Kit (Yuanqi, Shanghai, China). A 129-bp fragment spanning the catalytic domain of *IDH1* including codon 132 was amplified by using the sense primer *IDH1*f 5′-CGGTCTTCAGAGAAGCCATT-3′ and the antisense primer *IDH1*r 5′-GCAAAATCACATTATTGCCAAC-3′, as described previously.[13,14] Sequences were determined by using an ABI 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Image analysis

VASARI scoring of conventional MRI

The VASARI features were interpreted by two experienced neuroradiologists who were blinded to the histopathological subtypes based on precontrast and contrast-enhanced T1WI, T2WI, FLAIR, and DWI images. Twelve VASARI parameters were recorded, which included tumour location, side of tumour epicentre, enhancement quality, proportion enhancing, proportion non-enhancing, proportion necrosis, cysts, thickness of enhancing margin, definition of enhancing margin, proportion of oedema, haemorrhage, and diffusion. These VASARI features were chosen as they were considered to have a high level of reproducibility and could provide significant information for the diagnosis of gliomas according to previous studies.[15,16] In cases of interobserver disagreement regarding the score, one senior neuroradiologist helped to reach a consensus.

TA of DWI

T2WI and ADC map were registered to the contrast-enhanced T1WI.Regions of interest (ROIs) were manually drawn by a radiologist with 3 years of experience in neuroimaging research by using in-house software (Omnikinetics, GE Healthcare, China). Tumour ROIs were defined on the contrast-enhanced T1WI as areas of abnormal enhancement and non-enhancing tumour portion. Vessels, necrosis, and peritumour oedema were excluded according to T2WI. The three-dimensional (3D) volumes of interest (VOIs) were constructed by summing ROIs drawn in each section of co-registered contrast-enhanced T1WI and copied to the ADC map. The final VOI was approved by a senior neuroradiologist. A total of 56 texture features were then extracted from the ADC maps, which included 14 first-order parameters, 13 histogram-based parameters, 13 texture features from the grey-level co-occurrence matrix (GLCM) and 16 texture features from the grey-level run-length matrix (GLRLM).

Statistical analysis

The variables are presented as mean ± standard deviations (SDs). The Kappa test was applied to assess the consistency between the readers on the VASARI scoring. The Chi-square test or Fisher's exact test was used to compare the VASARI features of the *IDH1* mutation and wild-type as appropriate. The texture parameters were compared between the *IDH1* mutation and wild-type using unpaired Student's *t*-test or Mann–Whitney *U*-test as appropriate. The receiver operating characteristic (ROC) and logistic regression analysis were performed to determine the diagnostic performance of MRI and TA of ADC independently and in combination to discriminate *IDH1*-mutant from wild-type tumours. The area under the ROC curve (AUC), sensitivity, and specificity were calculated at a cut-off point. All statistical analyses were performed with statistical packages (SPSS, version 24.0, Chicago, IL, USA; MedCalc for Windows, version 13.1.2, Mariakerke, Belgium). $p<0.05$ was considered to indicate a statistically significant difference.

Results

The clinical, histological characteristics are summarised in Table 1. *IDH1* wild-type AGs were more common in patients aged >50 years at diagnosis than *IDH1*-mutant AGs ($p=0.038$). The inter-reader agreements for all the VASARI features were good to excellent (kappa value = 0.653–1.000). The 12 VASARI imaging features are detailed in the Electronic Supplementary Material Table S1. Statistically significant differences between the *IDH1*-mutant and wild-type tumours were found in enhancement quality, proportion enhancing, proportion non-enhancing, definition of enhancing margin, and proportion of oedema ($p<0.05$ for all). The best single VASARI feature for the present dataset was the proportion of the tumour that was non-enhancing (AUC=0.918; Table 2, Fig 1a). The proportion non-enhancing was significantly higher in *IDH1*-mutant AGs than that in wild-type AGs ($p<0.001$, odds ratio=14.25; Figs 2 and 3).

IDH1 genotype prediction using TA of DWI achieved great diagnostic efficiency. The TA features was detailed in Electronic Supplementary Material Table S2. The best single feature for the present dataset was entropy of the ADC map (AUC=0.724) (Table 2, Fig 1b). The entropy of ADC was higher in *IDH1*-mutant AGs than in wild-type AGs ($p=0.010$, odds ratio=6.015). The results of the ROC analysis are shown in Table 3 and Fig 4. According to the multivariable logistic regression analysis, a combination of MRI and TA of

Table 1
IDH1 mutation status of patients with anaplastic gliomas.

Characteristics	*IDH1* status			
	Total (n=46)	Mutant (n=21)	Wild-type (n=25)	p-Value
Age (years)	47.8±12.0	45.45±9.47	50.24±13.70	0.097[a]
≥50/<50	19:27	5:16	14:11	0.038[b]
Sex	24:22	9:12	15:10	0.375[b]
Male/female				
Histopathology	24/22	11/10	13/12	1.000[b]
AA/AO				

Significant difference between groups (p<0.05).
AA, anaplastic astrocytomas; AO, anaplastic oligodendrogliomas.
[a] The difference between the two groups was evaluated using the unpaired Student's t-test.
[b] The difference between the two groups was evaluated using the chi-square test.

Table 2
Prediction for *IDH1*-mutation status in anaplastic gliomas (AGs) using VASARI imaging and texture analysis (TA) of apparent diffusion coefficient (ADC) on multivariable logistic regression.

		IDH1 mutation	*IDH1* wild-type	p-Value	Odds ratio[a]
Proportion	2 = none (0%)	0	0	<0.001[b]	14.255
non-enhancing	3 = <5%	0	12 (48%)		
	4 = 6–33%	2 (9.5%)	8 (32%)		
	5 = 34–67%	10 (47.6%)	5 (20.05%)		
	6 = 68–95%	9 (42.9%)	0		
ADC entropy		5.843±0.431	5.334±0.876	0.010[c]	6.015

Data are number (%) unless otherwise indicated.
[a] Odds ratio for *IDH1*-mutant in AGs.
[b] The difference between the two groups was evaluated using the Mann–Whitney U-test.
[c] The difference between the two groups was evaluated using the chi-square test.

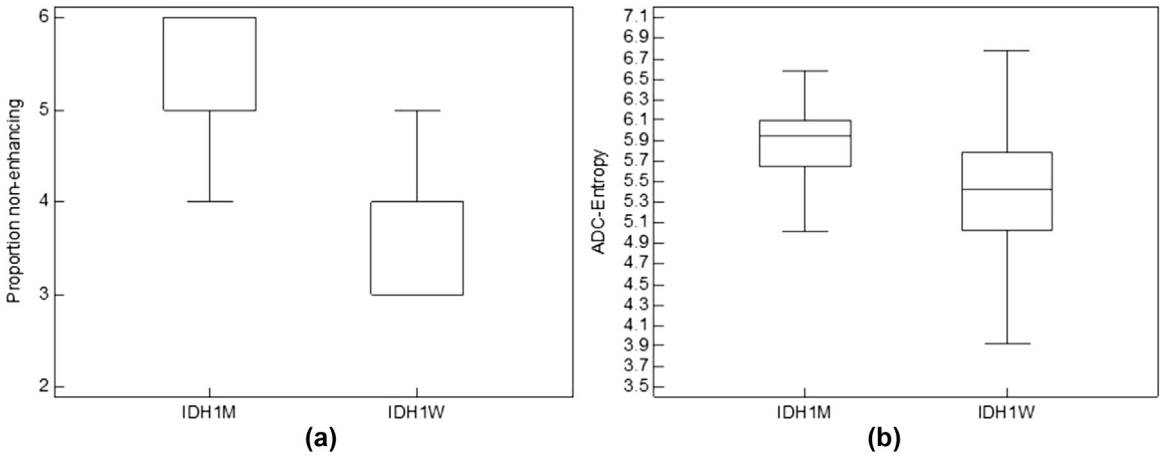

Figure 1 Plots of Proportion non-enhancing (a), Entropy of ADC (b), in patients with *IDH1*-mutant (*IDH1M*) anaplastic astrocytomas from and types (*IDH1W*). The proportion non-enhancing and entropy of ADC were significantly higher in patients with *IDH1*M compared with those with *IDH1*W (P < 0.05 each).

DWI for the diagnosis of *IDH1* mutation yielded an AUC, sensitivity, and specificity of 0.954, 81%, and 96%, respectively, which was higher than the single analysis.

Discussion

Previous studies have suggested that gene expression might be a better predictor of key outcomes than histological classification.[4] Thus, non-invasively detecting the genetic characteristics before surgery is important for predicting the outcome and choosing the best therapy. The present study demonstrates that MRI and TA of DWI can be used to evaluate the *IDH1* mutational status in AGs and that a combination of MRI and TA further improves the diagnostic accuracy.

IDH1 wild-type tumours were more common in patients aged >50 years at diagnosis. This correlation between age and *IDH1* mutation status in AGs has also been reported by Lee *et al.*[3]Previous studies have shown that the presence of large portions of non-enhancement in glioblastomas is strongly associated with the *IDH1* mutation.[17,18] Wang *et al.*[1] retrospectively reviewed 216 patients with AGs and identified that patients with the *IDH1* mutation were less likely

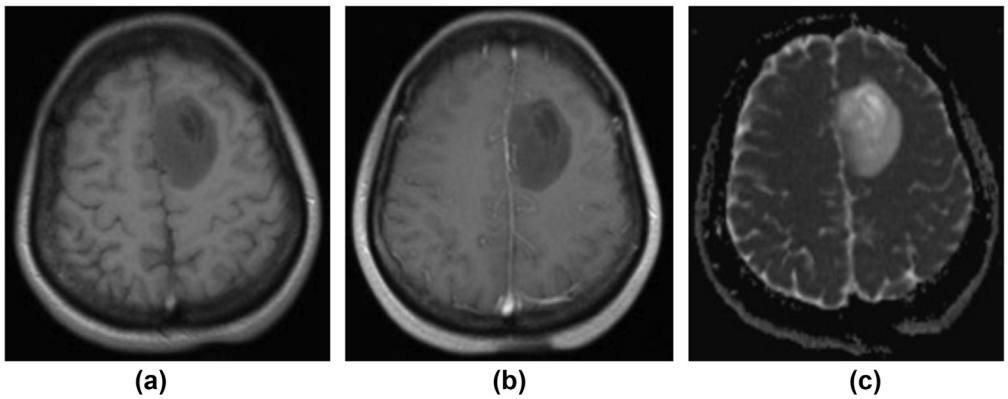

Figure 2 A 39- year-old woman with left frontal anaplastic astrocytoma. (a) axial T1-weighted image shows an well-defined heterogenous mass with slightly low signal intensity. (b) post-contrast axial T1-weighted image shows no obvious contrast enhancement (Proportion non-enhancing=6); (c) axial ADC map shows that there is no obvious restricted diffusion (ADC-Entropy=5.575).

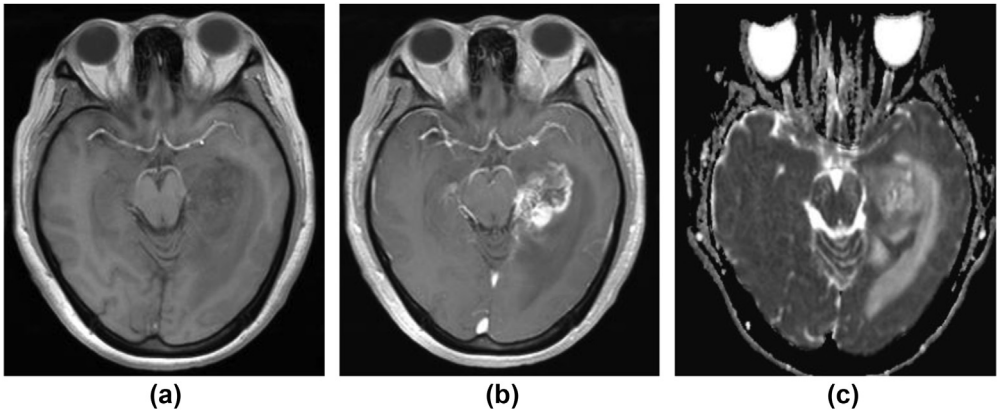

Figure 3 A 49-year-old female with left temporal anaplastic astrocytoma. (a) axial T1-weighted image shows an well-defined heterogenous mass with slightly low signal intensity. (b) post-contrast axial T1-weighted image shows partly obvious contrast enhancement (Proportion non-enhancing = 4); (c) axial ADC map shows that there is no obvious restricted diffusion (ADC-Entropy = 5.050)

Table 3
Receiver operating characteristic results of proportion of non-enhancement, of apparent diffusion coefficient (ADC) entropy, and magnetic resonance imaging (MRI) with texture analysis (TA) for assessing the *IDH1* status of anaplastic gliomas (AGs).

	AUC	Cut-off[a]	Sensitivity (%)	Specificity (%)
Proportion of non-enhancement	0.918 (0.799–0.978)	>4	90.5	80
ADC entropy	0.724 (0.572–0.845)	>5.763	71.4	76
Proportion of non-enhancement + ADC entropy	0.954 (0.848–0.994)	>0.615	81	96

Data in parentheses are 95% binomial exact confidence intervals.
[a] Cut-off value for identifying *IDH1*-mutant AGs.

to have tumour enhancement than those with wild-type *IDH1*. In the present study, a significant association between proportion non-enhancing and *IDH1*-mutated AGs was observed, which was consistent with previous studies. Moreover, previous studies reported that *IDH1*-mutation tumours are strongly associated with frontal locations.[20] In the present study, tumour location was not a significant predictor of *IDH1* mutation, which may be associated with the small number of cases. Although the radiological appearance of AGs was associated with *IDH1* mutation status, these MRI characteristics lack the ability to quantify the findings.

In the present study, multivariable TA extracted from the ADC map achieved diagnostic efficiency in predicting *IDH1* mutation in AGs. Previous studies have reported that MR spectroscopy is a promising method to help predict *IDH*-mutated tumours non-invasively.

2-Hydroxyglutarate (2-HG) is not detectable under normal conditions, when the concentration is too low; however, with the accumulation of 2-HG in *IDH* mutations, the concentration can increase >100-fold and can reach levels at which it can be detected; however, it is challenging to reliably detect *in vivo* because the 2-HG spectrum largely overlaps with abundant brain metabolites.[5] Pope *et al.*[21]

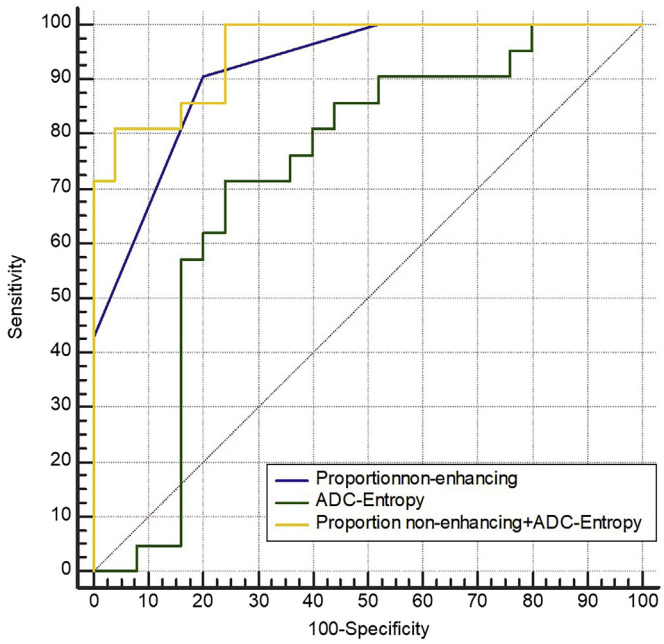

Figure 4 Comparison of receiver operating characteristic curves of Proportion non-enhancing, DWI-Entropy, cMRI+TA in differentiating *IDH1*-mutant anaplastic astrocytomas from wild types.

indicated that the specificity of 2-HG detection may be challenging and reported a false-positive rate of 26%. In comparison to previous studies that relied on complete MRI[19,20,22] or advanced imaging techniques,[23–25] the present results demonstrated the ability of a non-invasive method to achieve reliable prediction of *IDH1* mutation in AGs with very few preoperative MRI texture features. TA assesses the distribution of grey-levels within an image to obtain texture features of intra-lesion heterogeneity, which may be useful for a deeper analysis of the tumour.[26] The ADC value has been considered an index of tumour cellularity. Previous studies have reported the TA of the ADC map can be useful for evaluating glioma grade, which provides tumour heterogeneity.[11] Dang *et al.*[27] indicated that mutation in the *IDH* gene family could reduce catalytic generation of α-ketoglutarate and, in turn, lead to the production of the oncometabolite (R)-2HG, ultimately giving rise to increased cell proliferation or cellularity. Therefore, it is conceivable that differences in ADC value might be useful for predicting the molecular profile in astrocytomas with respect to *IDH* mutational status. In the present study, the TA of the ADC map can non-invasively assess *IDH1* mutational status in AGs, and the multivariable logistic regression model demonstrated that the entropy of the ADC was the best single-feature. *IDH1* mutated AGs showed statistically higher entropy of ADC than *IDH1* wild-type AGs, which can be interpreted as *IDH1*-mutated gliomas having a higher chance of exhibiting heterogeneous lesions than *IDH1* wild-type gliomas. This result suggested that the entropy of ADC can be further utilised as a quantitative and objective indicator for predicting *IDH1* status. Kinoshita *et al.*[10] presented T2WI TA for grade II and III gliomas, and the entropy on T2WI showed statistically lower Shannon entropy on T2WI in *IDH1* wild-type gliomas than *IDH1* mutated gliomas, which also indicated that *IDH1* wild-type gliomas are more homogeneous than *IDH1* mutated gliomas. The present study demonstrated that the minimum intensity and mean value of ADC were higher in *IDH1* mutation than in the wild-type, which reflected the sites of highest cellularity within heterogeneous *IDH1*-mutated AGs. These results were consistent with Xing *et al.*[25] and Lee *et al.*[3]; however, the entropy of ADC, which was the significant variable in the present study, showed higher diagnostic value than in the study of Lee *et al.*[3] The improvement maybe due to more features of gliomas extracted by TA method.

A combination of MRI and TA of ADC for the diagnosis of *IDH1* mutation yielded an AUC, sensitivity, and specificity of 0.954, 81%, and 96%, respectively, which improved the AUC and specificity and was better than any single feature or combination of other classifiers. In the present study, *IDH1*-mutated AGs were found to correlate with a higher proportion non-enhancement and entropy of ADC, which correspond to low levels of angiogenesis and higher heterogeneous lesions. This should be the pathology background for *IDH1* mutations AGs as they are less aggressive than *IDH1* wild-type AGs.

The present study has some limitations. First, the sample size is small, and a larger validation cohort is needed to validate the present approach. Second, there were other multiple genetic alterations (such as vascular endothelial growth factor, epidermal growth factor receptor, oxygen-6-methylguanine-DNA methyl transferase promoter methylation) in astrocytoma, which were related to the imaging characters. In this study, the focus was the *IDH1* gene to decrease the influencing factors. With an increase in cases, the imaging characters of astrocytoma with multiple gene abnormal expressions should be studied. In addition, this was a retrospective study, which may have the possibility of population bias and the results need be tested by a prospective study.

In conclusion, compared with *IDH1* wild-type tumours, *IDH1*-mutant tumours tend to have a higher proportion of non-enhancement in the tumour and higher entropy of ADC. Application of MRI combined with TA of DWI may provide an important and non-invasive marker to predict *IDH1* mutational status in AGs.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crad.2018.10.002.

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